

Experiment Number: S0594
Route: IV, Dosed Feed
Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary
Compound: Phenolphthalein / Analyte: Phenolphthalein
CAS Number: 77-09-8

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: RTI

Male

Treatment Group (mg/kg, ppm)

25 IV Plasma^{a,c}

200 Dosed Feed Plasma^{b,d}

375 Dosed Feed Plasma^{b,e}

Cmax_obs (ug/mL)	60.1 ± 14	.	0.0445 ± 0.035
AUC_0-T (ug*hr/mL)	19.8 ± 0.27	.	0.226 ± 0.045

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Treatment Group (ppm)

750 Dosed Feed Plasma^{b,f} 3000 Dosed Feed Plasma^{b,e} 12000 Dosed Feed Plasma^{b,e}

Cmax_obs (ug/mL)	0.0458 ± 0.012	0.192 ± 0.12	0.330 ± 0.020
AUC_0-T (ug*hr/mL)	0.739 ± 0.021	2.19 ± 0.18	6.27 ± 1.7

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Treatment Group (mg/kg, ppm)

25 IV Plasma^{a,c}

200 Dosed Feed Plasma^{b,d}

375 Dosed Feed Plasma^{b,e}

Cmax_obs (ug/mL)	61.1 ± 17	.	0.0590 ± 0.065
AUC_0-T (ug*hr/mL)	18.3 ± 0.090	.	0.181 ± 0.077

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750 Dosed Feed Plasma^{b,e} 3000 Dosed Feed Plasma^{b,e} 12000 Dosed Feed Plasma^{b,e}

Cmax_obs (ug/mL)	0.133 ± 0.19	0.445 ± 0.18	0.324 ± 0.37
AUC_0-T (ug*hr/mL)	0.910 ± 0.30	3.46 ± 0.23	4.17 ± 0.29

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Toxicokinetics Data Summary

Request Date: 7/11/2023

Route: IV, Dosed Feed

Compound: Phenolphthalein / Analyte: Phenolphthalein Glucuronide

Request Time: 10:03:16

Species/Strain: Mouse/B6C3F1

CAS Number: 77-09-8

Lab: RTI

Male

Treatment Group (mg/kg, ppm)

25 IV Plasma^{a,g}

200 Dosed Feed Plasma^{b,e}

375 Dosed Feed Plasma^{b,e}

Cmax_obs (ug/mL)	179 ± 23	26.7 ± 3.9	63.3 ± 3.3
AUC_0-T (ug*hr/mL)	680 ± 18	486 ± 12	1160 ± 31

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CAS Number: 77-09-8

Lab: RTI

Male

Treatment Group (ppm)

750 Dosed Feed Plasma^{b,e} 3000 Dosed Feed Plasma^{b,e} 12000 Dosed Feed Plasma^{b,e}

Cmax_obs (ug/mL)	102 ± 9.3	244 ± 29	406 ± 35
AUC_0-T (ug*hr/mL)	1961 ± 49	4502 ± 80	7494 ± 158

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Female

Treatment Group (mg/kg, ppm)

25 IV Plasma^{a,g}

200 Dosed Feed Plasma^{b,e}

375 Dosed Feed Plasma^{b,e}

Cmax_obs (ug/mL)	204 ± 20	49.4 ± 1.2	97.2 ± 15
AUC_0-T (ug*hr/mL)	901 ± 22	839 ± 22	1682 ± 38

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Treatment Group (ppm)

750 Dosed Feed Plasma^{b,e} 3000 Dosed Feed Plasma^{b,e} 12000 Dosed Feed Plasma^{b,e}

Cmax_obs (ug/mL)	148 ± 2.9	299 ± 17	422 ± 30
AUC_0-T (ug*hr/mL)	2589 ± 41	5772 ± 108	8770 ± 137

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LEGEND

MODELING SOFTWARE

Excel, Version 7

MODELING METHOD & BEST FIT MODEL

^a Excel, Version 7 used to calculate means and standard deviation for C_{max}, C_{max} steady state and AUC_{24-hr} by trapezoidal rule. Due to the extensive enterohepatic recycling of PTH, classical pharmacokinetic models are not applicable to the calculation of clearance, bioavailability, and other pharmacokinetic parameters for PTH.

^b Excel, Version 7 used to calculate means and standard deviation for C_{max}, C_{max} steady state and AUC_{24-hr} by trapezoidal rule. To determine AUC_{24-hr}, it was assumed that plasma concentrations of PTH and PTH-G in the 10 a.m. sample on day 14 were the same as those in plasma at 10 a.m. on day 15. Mean daily dose is 38.17 mg/kg/day. Due to the extensive enterohepatic recycling of PTH, classical pharmacokinetic models are not applicable to the calculation of clearance, bioavailability, and other pharmacokinetic parameters for PTH.

EXCEPTIONS

^c C_{max} at 2.5 minute timepoint

^d Not detected. All 3 triplicates were below the limit of detection (LOD) of 0.0012 ug/mL

^e It was assumed that after 14-15 days of continuous exposure to PTH in feed, plasma PTH and PTH-G concentrations were at steady state. (C_{max} ss)

^f Only four time points were detected. It was assumed that after 14-15 days of continuous exposure to PTH in feed, plasma PTH and PTH-G concentrations were at steady state. (C_{max} ss)

^g C_{max} at 5 minute timepoint

ANALYTE

Phenolphthalein

Phenolphthalein/Phenolphthalein Glucuronide

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TK PARAMETERS

C_{max_obs} = Observed or Predicted Maximum plasma (or tissue) concentration

AUC_{0-T} = Area under the plasma concentration versus time curve, AUC, from time t_i (initial) to t_f (final), AUC_{last}

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Extracted plasma samples were analyzed by High Performance Liquid Chromatography (HPLC) with a UV detector (230 nm) using bromocresol purple as the internal standard. Plasma PTH concentration at time zero was back extrapolated using the first two timepoints (2.5 and 5 minutes) after dose administration for AUC_{24-hr}. Plasma PTH-G concentration at time zero was assumed to be zero. AUC_{24-hr} was calculated using the trapezoidal rule for plasma concentrations from time zero to 24 hours.

TK_INTRAVENOUS PLASMA

25 mg/kg Male and Female

Animals received a single intravenous dose. Rats were sampled twice. 3 animals/species/sex/dose per timepoint. 15 timepoints 24 rats and 45 mice per group.

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TK_PARAMETERS PROTOCOL (cont'd)

ANALYSIS METHOD

Extracted plasma samples were analyzed by High Performance Liquid Chromatography (HPLC) with a UV detector (230 nm) using bromcresol purple as the internal standard. Cmax values are mean plus or minus standard deviations with n equal to 3.

TK_DOSED FEED PLASMA

200 ppm, 375 ppm, 750 ppm, 3000 ppm, 12000 ppm Male and Female

For multiple dose feed studies, rats and mice received dosed feed for 14-15 days. Plasma samples were collected at 2 hour intervals for 22 hours from 10 a.m. on day 14 through 8 a.m. on day 15. Three animals/species/sex/dose per timepoint (12 timepoints). Mouse Studies C-R and H-R shown as Cr and Hr are repeat studies. Extra animals are included in body weight calculations. Number of animals is 36 except for Study N which had 35 animals.